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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,649	07/09/2003	Judy H. Chiao	24852-501 CIP2	9975

35437 7590 09/20/2007

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
09/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,649	CHIAO ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-10,12-34 and 36-276* is/are pending in the application.

4a) Of the above claim(s) *2-5,20-33 and 48-270* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-10,12-19,34,36-47 and 271-276* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-5, 7-10, 12-34, AND 36-276 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 5/10/2007 and Information Disclosure Statements filed 4/18/2007 and 5/23/2007 have been received and entered into the application. Accordingly, claims 1, 7-10, 12-15, 18-19, 34, 36, 38-43, and 46-47 have been amended, claims 6, 11, and 35 have been cancelled, and claims 271-276 have been added. Also, as reflected by the attached, completed copy of USPTO Form 1449 the cited references have been considered.

Applicants' arguments, filed 5/10/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Election/Restrictions

Claims 2-5, 20-33, and 48-270 remain withdrawn from further consideration pursuant to 37 CFR § 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Accordingly, claims 1, 7-10, 12-19, 34, 36-47, and 271-276 are presently under examination and are the subject of this Office Action.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) or under 35 U.S.C. § 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e) and 35 U.S.C. § 120 as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/361,759 (filed 3/4/2002), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of this application.

The instantly claimed invention is drawn to the treatment of cutaneous T-cell lymphoma in a subject comprising orally administering a total daily dose of 200-600 mg of the histone deacetylase inhibitor, SAHA.

The disclosure of U.S. Provisional Application No. 60/361,759, filed 3/4/2002, is drawn to the use of histone deacetylase inhibitors, including the instantly claimed SAHA (page 7), for inducing terminal differentiation of neoplastic cells (page 9). The invention disclosed in the '759 application also provides a method of treating a patient "having a tumor" comprising administering an effective amount of any of the compounds disclosed therein (page 10). The

term tumor, as used in the '759 application, is defined as any cancer caused by the proliferation of neoplastic cells, "such as lung cancer, acute lymphoid myeloma, Hodgkins lymphoma, non-Hodkins lymphoma, bladder melanoma, renal carcinoma, breast carcinoma, prostate carcinoma, ovarian carcinoma, or colorectal carcinoma" (page 11). The treatment of cutaneous T-cell lymphoma is not explicitly disclosed. With respect to the instantly claimed oral administration of a total daily dose of 200-600 mg, the '759 application only discloses that the administration of the compound to the patient "may be effected orally or pareterally" (page 11). Intravenous administration is exemplified and doses for intravenous administration are disclosed. The instantly claimed 200-600 mg daily dose is not suggested or disclosed in the '759 application. Accordingly, the instantly claimed oral administration of a total daily dose of 200-600 mg SAHA is not supported by the '759 application.

In light of the above, the instantly claimed methods of treating cutaneous T-cell lymphoma in a subject comprising orally administering a total daily dose of 200-600 mg of the histone deacetylase inhibitor, SAHA, are afforded a priority date of 3/4/2003, the filing date of the 10/379,149 application, of which the present application is a continuation-in-part.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 12-19, 34, 40-47, and 271-276 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Breslow *et al.* (U.S. Patent No. 6,087,367; Issued Jul. 11, 2000) (prior art of record) in view of Curley *et al.* (Proceedings of ASCO, 2002, vol. 21, page 6b, entry 1831) (prior art of record)[1] and Piekarz *et al.* (Blood, 2001, vol. 98, pages 2865-2868) (prior art of record).

The instant claims recite the treatment of cutaneous T-cell lymphoma in a subject comprising orally administering a total daily dose of 200-600 mg of the histone deacetylase inhibitor, SAHA. Dependent claims recite specific doses within the broad range as well as specific administration schedules.

Breslow *et al.* teach methods of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells (Abstract). The invention also provides a method of treating patients having tumors comprising administering to said patient a compound of the invention (Abstract; col. 2, lines 44-47; col. 11, line 60 to col. 12, line 17). The compounds disclosed in Breslow *et al.* include the instantly claimed SAHA (col. 7, lines 1-42;

[1] Curley *et al.* qualifies as prior art under 35 U.S.C. § 102(a) because the instantly claimed oral administration of a total daily dose of 200-600 mg is not supported by Applicants' prior-filed Non-Provisional application (filed 3/4/2002).

col. 26, line 55 to col. 27, line 24; Table 1, Compound 3). Administration of the disclosed compounds may be effected orally or parenterally (col. 11, line 67 to col. 12, line 1). Breslow *et al.* do not expressly disclose the instantly claimed oral doses of SAHA or the specific treatment of cutaneous T-cell lymphoma.

However, Curley *et al.* teach that the histone deacetylase inhibitor, SAHA, has good bioavailability and biologic activity when orally administered. A new oral formulation of SAHA was escalated in patients from 200 mg daily, 400 mg daily, 400 mg BID (twice a day), 800 mg BID, 1200 mg BID, 1600 mg BID, and 2000 mg BID (Abstract). Accordingly, the authors conclude that oral administration of SAHA is feasible and does have biologic activity (*id.*).

With respect to the treatment of cutaneous T-cell lymphoma, Piekarz *et al.* teach that the depsipeptide, FR901228, a histone deacetylase inhibitor, is an effective treatment for this cancer (Abstract). The case report suggests that "depsipeptide, and potentially other [histone deacetylase inhibitors] may be effective in T-cell lymphomas" (page 2567). The authors also report that recent studies have shown that histone deacetylase inhibitors have activity against acute myeloid leukemia cell lines (*id.*).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art

In the instant case, Breslow *et al.* teach the instantly claimed SAHA, suggest that it may be administered orally, and further suggest and motivate the use of SAHA and related compounds in methods of treating tumors. Curley *et al.* teach that oral administration of SAHA, in doses ranging from 200 daily to 2000 mg twice a day, is biologically active and exhibits good bioavailability. Piekarz *et al.* demonstrate that a histone deacetylase inhibitor is a safe and effective treatment for patients having cutaneous T-cell lymphoma.

Differences Between Prior Art and Claims

The instantly claimed methods appear to differ from the methods taught in Breslow *et al.* in that the specific treatment of cutaneous T-cell lymphoma in the oral doses instantly claimed are not explicitly taught in the reference. Further, one must select SAHA from a list of disclosed compounds in Breslow *et al.* While Breslow *et al.* suggest and motivate the treatment of tumors in human patients, cutaneous T-cell lymphoma is not disclosed and the reference does not explicitly disclose any oral doses. However, Curley *et al.* suggest and motivate the instantly claimed oral doses of SAHA and further teach that such doses have biological activity.

Level of Ordinary Skill in the Art

A person having ordinary skill in the art at the time of the present invention would generally be a physician with several years of experience in drug administration.

Objective Evidence and Motivation

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to administer the histone deacetylase inhibitor, SAHA, to treat cutaneous T-cell lymphoma in the oral doses instantly claimed. See, *e.g.*, *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)). Considering the size of the prior art genus with respect to the limited number of compounds contemplated by Breslow *et al.*, one skilled in the art could readily envisage using SAHA to treat solid tumors. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962). In fact, Breslow *et al.* also expressly exemplify SAHA as a specific compound useful in the methods disclosed therein.

With respect to the instantly claimed oral administration, Curley *et al.* suggest and motivate the instantly claimed oral doses of SAHA and further teach that such doses have biological activity. Thus, one skilled in the art would reasonably expect that SAHA, as taught in Breslow *et al.* for the treatment of solid tumors, could be effectively orally administered in the instantly claimed dose ranges.

Finally, the instant claims recite the specific treatment of cutaneous T-cell lymphoma. However, Piekarz *et al.* demonstrate that a histone deacetylase inhibitor is a safe and effective treatment for patients having cutaneous T-cell lymphoma. Accordingly, the skilled artisan would have been imbued with at least a reasonable expectation that the histone deacetylase inhibitor SAHA would also be effective in treating cutaneous T-cell lymphoma. Such a reasonable expectation of success is further solidified by Breslow *et al.*, who teach and motivate the

treatment of solid tumors with SAHA and related compounds via induction of terminal differentiation of neoplastic cells.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to treat cutaneous T-cell lymphoma by orally administering SAHA in the doses and administration regimens instantly claimed. Firstly, it is the Examiner's position that Breslow *et al.* motivate the treatment of cancer, especially solid tumors, by administering compounds such as SAHA. Oral administration of the compounds of the invention is also suggested as an effective administration route for the disclosed compounds. Secondly, Curley *et al.* suggest and motivate the oral administration of SAHA in doses within the range instantly claimed. Although the administration disclosed in Curley *et al.* was not for the treatment of cutaneous T-cell lymphoma, one skilled in the art would have been motivated to use the oral doses disclosed in Curley *et al.* to treat the solid tumors as suggested and motivated by Breslow *et al.* Finally, with respect to treating cutaneous T-cell lymphoma, while the skilled artisan would recognize that the tumors disclosed in Breslow *et al.* are not an exhaustive list of tumors that may be treated with the compounds of the invention, Piekarz *et al.* provide the skilled artisan with at least a reasonable expectation that the methods of Breslow *et al.* would also be effective in treating cutaneous T-cell lymphoma. This is because the combined references clearly teach that: 1) SAHA may be effective in the treatment of solid tumors, including treatment via oral administration (Breslow *et al.*); 2) SAHA is a histone deacetylase inhibitor that is orally bioavailable and biologically active in the doses instantly claimed (Curley *et al.*); and 3) a histone deacetylase inhibitor has been demonstrated to be effective in the treatment of cutaneous T-cell lymphoma.

Thus, the skilled artisan would have been imbued with at least a reasonable expectation that cutaneous T-cell lymphoma could be effectively treated by oral administration of SAHA to patients having cutaneous T-cell lymphoma.

Claims 7-10 and 36-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Breslow *et al.* (U.S. Patent No. 6,087,367; Issued Jul. 11, 2000), Curley *et al.* (Proceedings of ASCO, 2002, vol. 21, page 6b, entry 1831) and Piekarz *et al.* (Blood, 2001, vol. 98, pages 2865-2868) (prior art of record) as applied to claims 1, 12-19, 34, 40-47, and 271-276 above, and further in view of Grant *et al.* (Pub. No. 2005/0004007 A1, based on the earlier U.S. filing date) (cited by Applicants in IDS filed 4/18/2007) and Kabadi (EP 0 547 000 A1) (cited by Applicants in IDS filed 4/18/2007).

Claims 7-10 and 36-39 of the instant application recite methods of orally administering a composition comprising SAHA, wherein the composition is contained in gelatin capsules and further comprises microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

Scope and Content of the Prior Art

Grant *et al.* teach oral administration (page 4, [0036]) of agents, which include the instantly claimed SAHA (page 5, [0039]). The reference also teaches soft or hard gelatin capsules for administration purposes (page 5, line 6). Grant *et al.* do not teach microcrystalline cellulose, croscarmellose sodium, and magnesium stearate as components of the pharmaceutical compositions disclosed therein.

However, Kabadi teaches a pharmaceutical composition for oral administration comprising fluvastatin (active ingredient), microcrystalline cellulose, croscarmellose sodium, and magnesium stearate (page 9, Example 4).

Differences Between Prior Art and Claims

The prior art does not expressly teach a composition for oral administration comprising SAHA, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Objective Evidence and Motivation

Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate are commonly used excipients in pharmaceutical compositions that are to be administered orally as evidenced by Kabadi. The above additives are well known to those skilled in the art as physiologically inactive ingredients that are added as a binder, disintegrant, and lubricant, respectively. One of ordinary skill in the art would find it obvious to use the claimed physiologically inactive ingredients taught in Kabadi in a pharmaceutical composition comprising SAHA for oral administration.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

September 13, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER